UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,731	01/06/2006	Else Marie Agger	PLOUG8.001APC	1203

20995 7590 07/23/2009

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
07/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,731	AGGER ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/10/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 6-23* is/are pending in the application.

4a) Of the above claim(s) *12,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-11,13-15 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 3-24-09. Claim 4 has been amended. Claims 12, and 16-17 have been withdrawn. Claims 18-23 are new claims. Claims 1-2, 4, and 6-23 are pending. Claims 1-2, 4, 6-11, 13-15, 18-23 are currently under examination.

Objections/Rejections Withdrawn

2. In view of the Applicant's amendment and remark following objections are withdrawn.

a) Objection to the drawings because Figures 6 and 9 have graphs with no data disclosed on them is withdrawn in light of applicant's argument.

b) Objection to claim 4 because the of the following informalities: As to claim 1, the claim contains the acronym DDA, DODA, DC-chol or DOTAP them is withdrawn in light of applicant's amendment.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The rejection of claims 8 and 10 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement are maintained for the reasons set forth in the previous Office Action. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph, March 24, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicants argue that undue experimentation is not required to combine the presently claimed adjuvant with known vaccines for cancer, allergy, or autoimmune disease so as to achieve a formulation that elicits an improved immune response. Applicants state that assays to determine whether such combinations produce an improved response are well known and that, investigators routinely provide varying vaccine formulations containing a wide-range of adjuvants to animals and human beings and rapidly analyze whether such varied formulations improve antibody production and/or cellular responses to the antigen.

B) Applicants provide herewith a copy of a paper that demonstrates that the claimed adjuvant improves the immune response to a wide-range of antigens (see Exhibit A). Applicants state the paper reports that the claimed adjuvant induced production of a strong immune response to Mycobacterium, Chlamydia, tetanus, and ovalbumin antigens (See abstract and Figures 2, 3, 5, and 6). As described in the originally filed specification, the presently claimed adjuvant improves the immune response to a wide range of antigens.

Examiner's Response to Applicant's Arguments:

In response to applicant's statement as set forth in (A), the claims are drawn to a vaccine comprising an adjuvant, comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium. Furthermore the claims are drawn to an improved vaccine for cancer, allergy, or an autoimmune disease. Although the specification does disclose *in vivo* methods of determining the immune response to an infection by *Mycobacteria bovis*, the examples and data (see pages 24-33) disclosed do not demonstrate that the composition confers "protection" against any pathogen generally or that composition confers "protection" against cancer, allergy, or an autoimmune disease. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The specification is devoid of any teaching that the claimed vaccine provides with any adjuvant a protective response against any subject and one of skill in the art would not know how use the invention as claimed. Therefore the rejection is not deemed persuasive.

In response applicants statement as set forth in (B), although Applicants provided a paper that demonstrates that the claimed adjuvant improves the immune response, the claims are specifically limited to a vaccine comprising an adjuvant and are not drawn to a method for stimulating an immune response and as set forth supra a vaccine by definition must provide

protection against an infection demonstrable by challenge experiments. The specification is devoid of any teaching that the claimed vaccine provides with any adjuvant a protective response against any subject and one of skill in the art would not know how use the invention as claimed. Therefore the rejection is not deemed persuasive.

As outlined previously, the specification is not enabled for any vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine for cancer, allergy, or an autoimmune disease, wherein the improvement comprises the adjuvant.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B)The nature of the invention;
(C)The state of the prior art;
(D)The level of one of ordinary skill;
(E)The level of predictability in the art;
(F)The amount of direction provided by the inventor;
(G)The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The claims are drawn to a vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine for cancer, allergy, or an autoimmune disease, wherein the improvement comprises the adjuvant.

Breadth of the claims: The claims are broadly drawn to a vaccine comprising any antigenic component comprising any antigenic epitope from a virulent mycobacterium species or

for an improved vaccine for any type of cancer, allergy, or any type of autoimmune disease, wherein the improvement comprises the adjuvant.

Guidance of the specification/The existence of working examples:

The specification discloses immunogenicity of various polar, apolar, and total lipid extracts and the ability of the total lipids/ DDA to induce immune responses of antigens from various sources (Table 6A pg. 27, and Tables 5-7 pgs. 26-29). The specification discloses antigen-specific antibody response in serum from Ag85-ESAT6 from immunized mice measured by ELISA (see Table 2 pg. 23). The specification discloses antibody response from mice immunized with various polar, apolar, and total lipid extract (see pg. 30 Table 8). The specification discloses an immune response generated with DDA/total lipids from different mycobacterial species by immunizing mice (see pgs. 25 Table 4 and pg. 31). The specification discloses the reduction of the bacterial load of *Mycobacteria BCG* comprising administering Ag85B-ESAT6 alone or Ag85B-ESAT6/DDA (antigenic epitope/adjuvant) in a mouse model (see pg. 21 Table 1).

Therefore the specification is only limited to an adjuvant that raises an antibody response and Ag85B-ESAT6/DDA (antigenic epitope/adjuvant) that also raises an antibody response and reduces the bacterial load of *Mycobacteria BCG.* The claimed invention is drawn to vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine for cancer, allergy, or an autoimmune disease, wherein the improvement comprises the adjuvant. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the composition confers "protection" against infection by *Mycobacteria* nor any type of cancer, allergy or autoimmune disease. The data merely shows that the adjuvant and Ag85B-ESAT6/DDA (antigenic epitope/adjuvant) increases an antibody response. Further more the data merely shows the reduction of a bacterial load of *Mycobacteria BCG* Ag85B-ESAT6/DDA (antigenic epitope/adjuvant). Therefore the data fails to show prevention or vaccine protection against cancer, allergy, or an autoimmune disease. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a preventing cancer, allergy, or an autoimmune disease as

claimed and the specification is devoid of any teaching that the claimed prevents cancer, allergy, or an autoimmune disease. Therefore, the specification as filed fails to provide particular guidance demonstrating a reasonable extrapolation, which resolves the known unpredictability in the art.

State of the art: The art discloses defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response (i.e. generation of an antibody that binds to a given epitope) can only be identified empirically (Greenspan et al. 1999 Nature Biotechnology 17: 936-937). The art as at the time of filing teaches that: Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrashekar et al., US Patent 6,248,329, col. 1, lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, et al. (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen. Furthermore, A vaccine “must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough.” In re Wright, 999 F.2d 1557,1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these

proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Sprott et al teach vaccine adjuvant properties of liposomes formed at elevated temperatures from the polar chloroform extractable lipids from mycobacterium bovis bacillus calmette-guerin to treat mycobacteria infections (see US Patent Application 20040191304 A1). However the art does not teach adjuvant to treat a vaccine comprising any antigenic component comprising any antigenic epitope from a virulent mycobacterium species or for an improved vaccine for any type of cancer, allergy, or any type of autoimmune disease, wherein the improvement comprises the adjuvant. Therefore the state of the art questions if a vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine can treat for cancer, allergy, or an autoimmune disease. For the reasons set forth supra, the state of the art has limitations to a vaccine aforementioned above and the state of the art is unpredictable with regard to any vaccine as set forth supra comprising an adjuvant.

In conclusion, the claimed inventions are not enabled for any vaccine comprising an antigenic component comprising an antigenic epitope from a virulent mycobacterium or for an improved vaccine for cancer, allergy, or an autoimmune disease, wherein the improvement comprises the adjuvant. The claims are broadly drawn to a vaccine comprising any antigenic component comprising any antigenic epitope from a virulent mycobacterium species or for an improved vaccine for any type of cancer, allergy, or any type of autoimmune disease, wherein the improvement comprises the adjuvant. The specification is only limited to an adjuvant that raises an antibody response and Ag85B-ESAT6/DDA (antigenic epitope/adjuvant) that also raises an antibody response and reduces the bacterial load of *Mycobacteria BCG*. The

specification is devoid of any teaching that the claimed prevents cancer, allergy, or an autoimmune disease. the state of the art has limitations to a vaccine aforementioned above and the state of the art is unpredictable with regard to any vaccine as set forth supra comprising an adjuvant. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 1, 4, 6-7, 10-11, and 13 under 35 U.S.C. 102(b) as being anticipated by Liu et al US Patent Application 20020044951 Date April 18, 2002 are maintained for the reason set forth in the previous office action.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 102(b), first paragraph, March 24, 2009 is carefully considered, but not found to be persuasive for the reasons below.

Applicants argue Liu et al. does not specifically disclose the particular combination of elements described by the Applicant. Applicants state in paragraph [0031], Liu et al., discloses a long list of examples of non-peptide antigens from M. tuberculosis including fractionated non-peptide compounds and specific antigens; whereas, in paragraph [0049] Liu et al. discloses that the lipid antigens may be formulated into liposomes, which may comprise a phospholipid. DOTAP,C1 is one of 25 phospholipids mentioned. Applicants state while Liu et al., states that the lipid antigens can be formulated into liposomes with adjuvants such as QS-21 and that the liposomes may comprise phospholipids including carrier phospholipids, including DOTAP; Liu et al. specifically states that their vaccine compositions are made by sonicating and/or vortexing the phospholipid carrier and lipid antigen or at a minimum extruding the mixture through a filter

of defined pore size (see paragraph 0051). Liu et al., further states that the "adjuvant" is then added after extrusion, i.e., after defined phospholipid vesicles containing the lipid antigens and carrier phospholipids are formed (Id.). Applicants state that accordingly, in the composition made by Liu et al., the adjuvant does not "comprise" the apolar fraction or part of a total lipid extract of mycobacterium, the lipid antigens are bound into phospholipids and the adjuvant is separate and apart from this structure.

Applicants also note that the compositions described in Liu et al. do not contemplate the incorporation of DDA, DODA, or Dc Chol or additional tuberculosis antigens, such as ESAT6-Ag85B hybrid or a fragment thereof.

Examiner's Response to Applicant's Arguments:

In response to the applicant's statement as set forth supra, while a genus does not always anticipate a species within the genus,when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the *Merck Index*, saying that "the tenth edition of the *Merck Index* lists ten thousand compounds. In our view, each and every one of those compounds is 'described' as that term is used in 35 U.S.C. § 102(a), in that publication."). *Id.* at 1718. (See MPEP 2131.02)

Therefore although Liu et al discloses a long list of examples, Liu et al discloses the instant invention. As to Applicants argument that their vaccine compositions are made by sonicating and/or vortexing the phospholipid carrier and lipid antigen or at a minimum extruding the mixture through a filter of defined pore size (see paragraph 0051). The claim is broadly drawn to a vaccine not process of making or using a vaccine. Although Lui et al does not contemplate the incorporation of DDA, DODA, or Dc Chol or additional tuberculosis antigens, such as ESAT6-Ag85B hybrid or a fragment thereof. The claim is broadly drawn to an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium. Liu et al teach an adjuvant comprising a cationic surfactant (DOTAP) (see [0049] and an apolar fraction or part

of total lipid extract of a mycobacterium (see abstract, [0031], [0059]). Liu et al teach antigens may be isolated from a lipid extract of M. tuberculosis, preferably the lipids may be crudely fractionated into purified nonpolar antigens(see 0031). Therefore the limitations have been met.

As outlined previously, the claims are drawn are drawn to an adjuvant comprising a cationic surfactant and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium (claim 1), a vaccine comprising the adjuvant (claim 6), wherein said vaccine is formulated for parenteral, oral or mucosal administration (claim 7), an improved vaccine for cancer, allergy or an autoimmune disease, wherein the improvement comprises the adjuvant (claim 10), a delivery system comprising the adjuvant (claim 11), wherein said mycobacterium is *BCG, M. microti, M. tuberculosis or M. vaccae* (claim 13).

Liu et al teach an adjuvant comprising a cationic surfactant (DOTAP) (see [0049] and an apolar fraction or part of total lipid extract of a mycobacterium (see abstract, [0031], [0059]). Lui et al teach a vaccine comprising the adjuvant, wherein vaccine is formulated for parenteral, oral or mucosal administration (see 0048, 0054). Liu et al teach an improved vaccine for an autoimmune disease, wherein the improvement comprises the adjuvant (see 0020-0028). Liu et al teach a delivery system comprising an adjuvant (see 0045). Liu et al teach an adjuvant wherein mycobacterium is *M. tuberculosis* (see claims).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The rejection of claims 1, 4, 6-11, 13 and 15 rejected under 35 U.S.C. 103(a) as being unpatentable by Liu et al US Patent Application 20020044951 Date April 18, 2002 in view of Anderson et al US Patent Application 20020176867 Date November 28, 2002 are maintained for the reasons set forth in the previous office action.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph, March 24, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicant's state that the discovery that a particular combination of surfactant and apolar fraction or part of a total lipid extract of a mycobacterium produced a synergistic immune response was surprising and unexpected and Table 1 of the specification shows that Ag85B-ESAT6 alone or combined with Ag85B-ESAT6/DDA are not capable of providing any notable protection against M. tuberculosis.

Applicants state that in contrast, administration of a combination of Ag85B-ESAT6/DDA/apolar fraction of the total lipid extract of a mycobacterium produces a synergistic immune response against M. tuberculosis and similar results were also obtained when using the total lipid extract or the polar fraction of the total lipid extract. Applicants state that however, the immune response obtained when using the total lipid extract or the polar fraction was different from that obtained with the apolar fraction. Applicants state that the apolar fraction produced a much higher interferon gamma response compared to that obtained when using the total lipid extract or the polar fraction (see Table 7) and all of the extracts produced antibodies (see Table 8). Applicant argue that unexpectedly, Applicants found that the combination of surfactant and apolar fraction or part of a total lipid extract of a mycobacterium produced a potent adjuvant that can potentiate the immune response to a co-administered antigen.

B) Applicants state that Liu et al., only contemplates using the apolar fraction or part of a total lipid extract of a mycobacterium as an antigen in conjunction with other adjuvants and carrier phospholipids. Applicants state Liu et al., prepares the compositions by sonicating/vortexing and extruding the preparation so as to create discretely sized liposomes, which are added to adjuvants.

C) Applicants argue that Andersen describes various antigenic components; for example, fusion proteins of the immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis, the inventors seek to develop potent single antigen vaccines (see paragraph 0010), specifically, the Ag85B-ESAT-6 fusion protein. Andersen et al. states that the 'in addition to being more cost- effective and less time consuming, the delivery of these selected molecules as a single fusion protein has the potential advantage of inducing amplified responses to molecules with a low inherent immunogenicity." (see paragraph 0016) . Accordingly, Andersen et al. teaches away from adding the ESAT-6 and Ag85B antigens into the milieu of antigens present in extracts as taught by Liu et al so as to arrive at the claimed invention.

Examiner's Response to Applicant's Arguments:

In response to applicants statements in (A), as to applicants discovery and tables disclosed in the specification as set forth supra, claims are broadly drawn to an adjuvant comprising a cationic surfactant and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium, not a specific cationic surfactant and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium as discussed in the specification and in the unexpected results.

In response to applicant's statements in (B), the claim utilizes the transitional phrase "comprising" which means the claims are not limited to the specific limitations recited in the claims. Furthermore the claims are not drawn to process of making or using. The claims are products by process claims and the patentability of a product does not depend on its method of production (see MPEP 2113). Therefore the claim are broadly drawn to an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium. Furthermore given that Liu et al teach antigens may be isolated from a lipid extract of M. tuberculosis, preferably the lipids may be crudely fractionated into purified nonpolar antigens (see 0031) and teach said antigens are immunogenic (see 0020-0028). It remains obvious to combine them with other adjuvants, even

without an express statement of motivation. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

In response to the applicants statements in (C), Examiner disagrees that Andersen et al teaches away from adding ESAT-6-Ag85B antigens. Andersen et al teach fusion proteins of the immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis and a tuberculosis vaccine based on the fusion proteins. One would be motivated to incorporate virulent mycobacteria (as disclosed Andersen et al) into a vaccine to clear or control an infection with virulent bacteria. One would have reasonable expectation of success because vaccine comprising adjuvants are well known in the art.

As outlined previously, the claims are drawn are drawn to an adjuvant comprising a cationic surfactant and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium (claim 1), a vaccine comprising the adjuvant (claim 6), wherein said vaccine is formulated for parenteral, oral or mucosal administration (claim 7), wherein the vaccine comprises an antigenic component comprising an antigenic epitope from a virulent mycobacterium (claim 8), wherein the antigenic component comprises an ESAT6-Ag85B hybrid or a fragment thereof (claim 9), an improved vaccine for cancer, allergy or an autoimmune disease, wherein the improvement comprises the adjuvant (claim 10), a delivery system comprising the adjuvant (claim 11), wherein said mycobacterium is *BCG, M. microti, M. tuberculosis or M. vaccae* (claim 13), wherein said virulent bacterium is selected from the group consisting of *M. tuberculosis, M. bovis and M. africanum* (claim 15).

Liu et al teach an adjuvant comprising a cationic surfactant (DOTAP) (see [0049] and an apolar fraction or part of total lipid extract of a mycobacterium (see abstract, [0031], [0059]). Lui et al teach a vaccine comprising the adjuvant, wherein vaccine is formulated for parenteral, oral or mucosal administration (see 0048, 0054). Liu et al teach an improved vaccine for an autoimmune disease, wherein the improvement comprises the adjuvant (see 0020-0028). Liu et al teach a delivery system comprising an adjuvant (see 0045). Liu et al teach an adjuvant wherein mycobacterium is *M. tuberculosis* (see claims).

Liu et al is relied upon as set forth supra. However Liu et al does not teach an adjuvant, wherein the vaccine comprises an antigenic component comprising an antigenic epitope from a virulent mycobacterium, wherein the antigenic component comprises an ESAT6-Ag85B hybrid or a fragment thereof, wherein said virulent bacterium is selected from the group consisting of *M. tuberculosis, M. bovis and M. africanum*.

Anderson et al teach a tuberculosis vaccine of immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis. Anderson et al teach a vaccine, wherein the antigenic component comprising an antigenic epitope from a virulent mycobacterium, wherein the antigenic component comprises an ESAT6-Ag85B hybrid, wherein said virulent bacterium is selected from the group consisting of M. tuberculosis (see title, abstract, claims, 0027, 0079, whole document in its entirety).

It would have been prima facie obvious at the time the invention was made to incorporate a virulent component as taught by Anderson et al into the adjuvant as taught by Liu et al because Liu et al and Anderson et al both teach vaccine composition to treat autoimmune diseases.

6. The rejection of claims 1, 2, and 14 rejected under 35 U.S.C. 103(a) as being unpatentable by Liu et al US Patent Application 20020044951 Date April 18, 2002 in view of Ravindranath et al US Patent No. 6218166 is maintained for the reasons set forth in the previous office action.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 103(a), March 24, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicants argue that the Ravindranath et al describes incorporating an adjuvant into or onto an intact cell. (see column 3, lines 28-32). Ravindranath et al., states that the use of whole cells is an important feature of the invention so as to insure that the antigens are presented in their natural environments and that any extraction method that removes the antigen from the membrane is likely to alter its immunogenic properties (see column 4, lines 13-24). Accordingly, Ravindranath et al., teaches away from applying the harsh conditions (i.e., sonication, vortexing, and extrusion) employed by Liu et al. or the evaporation approach used by the applicants to arrive at the claimed invention.

Examiner's Response to Applicant's Arguments:

In response to applicants statements, Examiner disagrees, Ravindranath et al. further teach any adjuvant may also be employed in this invention, so long as the adjuvant may be incorporated into an intracellular compartment, or incorporated onto, physically associated with, or conjugated to the cell membrane of the cell in question. Ravindranath et al. teach adjuvants may be provided as purified components, in a partially purified state, or even as a membrane preparation or cellular extract, so long as the active components of such compositions can be incorporated into the cell itself or associated with, integrated into, or conjugated to the membrane of the target cell. Ravindranath et al. teach using membrane preparations and cellular extracts is not considered to be a particular problem due to the physical properties of the adjuvants and the mechanisms of membrane integration. Furthermore given that Ravindranath et al. teach useful adjuvants that can be conjugated to cellular vaccines are whole or part of cell phenolic glycolipids (see Table 1). It remains obvious to incorporate phenolic glycolipids (as disclosed Ravindranath et al.) into an adjuvant because adjuvant-incorporated cell compositions are useful in methods to significantly improve immune responses and may be employed to stimulate or increase the antibody or T cell responses against intracellular or membrane-bound antigens, even those that are otherwise poor immunogens, even without an express statement of motivation. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

As outlined previously, the claims are drawn are drawn to an adjuvant comprising a cationic surfactant and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium (claim 1), wherein the part of the apolar fraction of the lipid extract is selected from the group consisting of phthiocerol dimycocerosates, trehalose mycolipenates, glycosylated phenol phthiocerols, thehalose mycolates, sulfolipids, triacylglycerols and menaquinones (claim 2), wherein said glycosylated phenol phthiocerols are phenolic glycolipids (claim 14).

Liu et al teach an adjuvant comprising a cationic surfactant (DOTAP) (see [0049] and an apolar fraction or part of total lipid extract of a mycobacterium (see abstract, [0031], [0059]). Lui et al teach a vaccine comprising the adjuvant, wherein vaccine is formulated for parenteral, oral

or mucosal administration (see 0048, 0054). Liu et al teach an improved vaccine for an autoimmune disease, wherein the improvement comprises the adjuvant (see 0020-0028). Liu et al teach a delivery system comprising an adjuvant (see 0045). Liu et al teach an adjuvant wherein mycobacterium is *M. tuberculosis* (see claims).

Liu et al is relied upon as set forth supra. However Liu et al does not teach an adjuvant, wherein the part of the apolar fraction of the lipid extract is selected from the group consisting of phthiocerol dimycocerosates, trehalose mycolipenates, glycosylated phenol phthiocerols, thehalose mycolates, sulfolipids, triacylglycerols and menaquinones, wherein said glycosylated phenol phthiocerols are phenolic glycolipids, wherein said virulent bacterium is selected from the group consisting of M. tuberculosis, M. bovis and M. africanum.

Ravindranath et al teach adjuvant-incorporated cell composition and methods for enhancing the antibody and T cell response to cellular antigens by incorporating an immunopotentiating agent into the cellular membrane or into an intracellular compartment to increase immune responses against.

Ravindranath et al teach an adjuvant, wherein part or whole of cell of Mycobacterial species of phenolic glycolipids wherein the part of the apolar fraction of the lipid extract is glycosylated phenol phthiocerols, wherein said glycosylated phenol phthiocerols are phenolic glycolipids.

Furthermore given that Ravindranath et al. teach useful adjuvants that can be conjugated to cellular vaccines are whole or part of cell phenolic glycolipids (see Table 1). It would have been prima facie obvious at the time the invention was made to incorporate a phenolic glycolipids as taught by Ravindranath et al into the adjuvant as taught by Liu et al, even without an express statement of motivation. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

New Grounds of Rejections

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 18-23 rejected under 35 U.S.C. 103(a) as being unpatentable by Liu et al US Patent Application 20020044951 Date April 18, 2002 in view of Andersen et al 1994 Vol. 62 No. 6 pgs. 2536-2544, Anderson et al US Patent Application 20020176867 Date November 28, 2002, Lowrie et al US Patent Application 20020198168 Date December 26, 2002.

Claims 18-23 are drawn to an immunogenic composition comprising an adjuvant and a tuberculosis antigen, wherein said adjuvant comprises a solution prepared from an evaporated mixture of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanumand a solvent (claim 18); wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof (claim 19); an adjuvant consisting essentially of a resuspension of an evaporated mixture of a solvent, a surfactant selected from the group consisting of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanumand a solvent (claim 20); comprising a tuberculosis antigen (claim 21), wherein said

tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof (claim 22), wherein surfactant is DDA (claim 23).

Liu et al teach an adjuvant comprising an apolar fraction or part of total lipid extract of a mycobacterium (see abstract, [0031], [0059]). Liu et al teach a delivery system comprising the an adjuvant (see 0045). Liu et al teach an adjuvant wherein mycobacterium is *M. tuberculosis* (see claims). Liu et al teach composition comprising an antigen isolated from *M. tuberculosis* (see abstract).

Liu et al differs from the instant invention in that they don't explicitly disclose an adjuvant comprising a solution prepared from an evaporated mixture of DDA, DODA, or Dc Chol, wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof, wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof, wherein said surfactant is DDA.

Anderson et al 1994 teach a vaccine against tuberculosis with DDA whereby the solution prepared was evaporated (see abstract and pg. 2537 column 1 last paragraph column 2 first paragraph.

Anderson et al teach 20020176867 a tuberculosis vaccine of immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis. Anderson et al teach a vaccine, wherein immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis (see abstract, claims, 0027, 0079, whole document in its entirety).

Lowrie et al teach nucleic acid constructs to be administered to present them as pharmaceutical formulations. Lowrie et al teach formulations comprise at least one active ingredient, a nucleic acid together with one or more acceptable carriers thereof. Lowrie et al teach the carrier or carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipients thereof. Lowrie et al teach liposomes may be used such as 3.beta.-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol (Dc-Chol) (see 0333).

It would have been prima facie obvious at the time the invention was made modify the composition to incorporate DDA whereby the solution prepared was evaporated (as disclosed Andersen et al 1994) into a composition in order to take advantage of effective vaccine against Mycobacterium tuberculosis.

One would have a reasonable expectation of success because to use DDA in an immunogenic composition (as disclosed Andersen et al 1994) is well known in the art.

It would have been prima facie obvious at the time the invention was made modify the composition to incorporate a tuberculosis vaccine of immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis (as disclosed Andersen et al 20020176867) into a composition in order to take advantage clearing or controlling an infection with virulent bacteria.

One would have reasonable expectation of success because to use ESAT-6 and Ag85B in an immunogenic compositions (as disclosed Andersen et al 20020176867) comprising adjuvants are well known in the art.

It would have been prima facie obvious at the time the invention was made modify the composition to incorporate DC-chol (as disclosed Lowrie et al) into a composition in order to take advantage of a liposome carrier that is acceptable in the sense of being compatible with the other ingredients of a formulation and not deleterious to the recipients thereof (see 0032).

One would have reasonable expectation of success because to use DC-Chol in an immunogenic compositions (as disclosed Liu et al) comprising adjuvants are well known in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite the phrase "are drawn to an immunogenic composition comprising an adjuvant and a tuberculosis antigen, wherein said adjuvant comprises a solution prepared from an evaporated mixture of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of

BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanumand a solvent (claim 18); wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof (claim 19)". Although Applicant filed an explanation in the Applicants Arguments/Remarks on 12/10/2008 stating support (see paragraphs 0010, 0016, 0020, 0029, 0039, and 0079) for the recitation set forth supra, these portions of the specification do not provide either explicit or implicit support for said limitation. Therefore, it is apparent, that Applicants were not in possession of the claimed recitations as set forth supra at the time of filing. Applicants pointing to the specification by page and line number where specific written description for the recitation set forth supra may resolve this issue. This is a new matter rejection.

10. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite the phrase "consisting essentially of a resuspension of an evaporated mixture of a solvent, a surfactant selected from the group consisting of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanumand a solvent (claim 20); comprising a tuberculosis antigen (claim 21), wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof (claim 22), wherein surfactant is DDA (claim 23)". Although Applicant filed an explanation in the Applicants Arguments/Remarks on 12/10/2008 stating support (see paragraphs 0010, 0016, 0020, 0029, 0039, and 0079) for the recitation set forth supra, these portions of the specification do not provide either explicit or implicit support for said limitation. Therefore, it is apparent, that Applicants were not in possession of the claimed recitations as set forth supra at the time of filing. Applicants pointing to the specification by page and line number where specific written description for the recitation set forth supra may resolve this issue. This is a new matter rejection.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645